Pharmaceuticals in the environment: scope of the problem

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Pharmaceuticals and personal care products (PPCPs)

- Human and veterinary drugs,
- Diagnostic agents (e.g., X-ray contrast media),
- "Nutraceuticals" (bioactive food supplements)
- Other consumer chemicals,
  - –fragrances (e.g., musk)
  - –sun-screen agents;
  - –"excipients" (so-called "inert" ingredients used in PPCP manufacturing and formulation).

PPCPs as an "Emerging" Problem?

- Not a new phenomenon; probably present as long as the chemicals have been made
- More widely evident because of lower detect limits, increased surveillance
- BUT, increasing concerns because of emerging concerns about low-dose effects in humans and wildlife.

Historical Perspective - PPCPs

- PPCPs as environmental pollutants first investigated in Europe - 1980s.
- In the U.S., literature has grown exponentially since 2000; understanding significance is beginning to develop.
- High public visibility.
- Involves expertise from various disciplines ranging from human health to ecology - - necessitating communication between the medical/healthcare communities and environmental sciences.

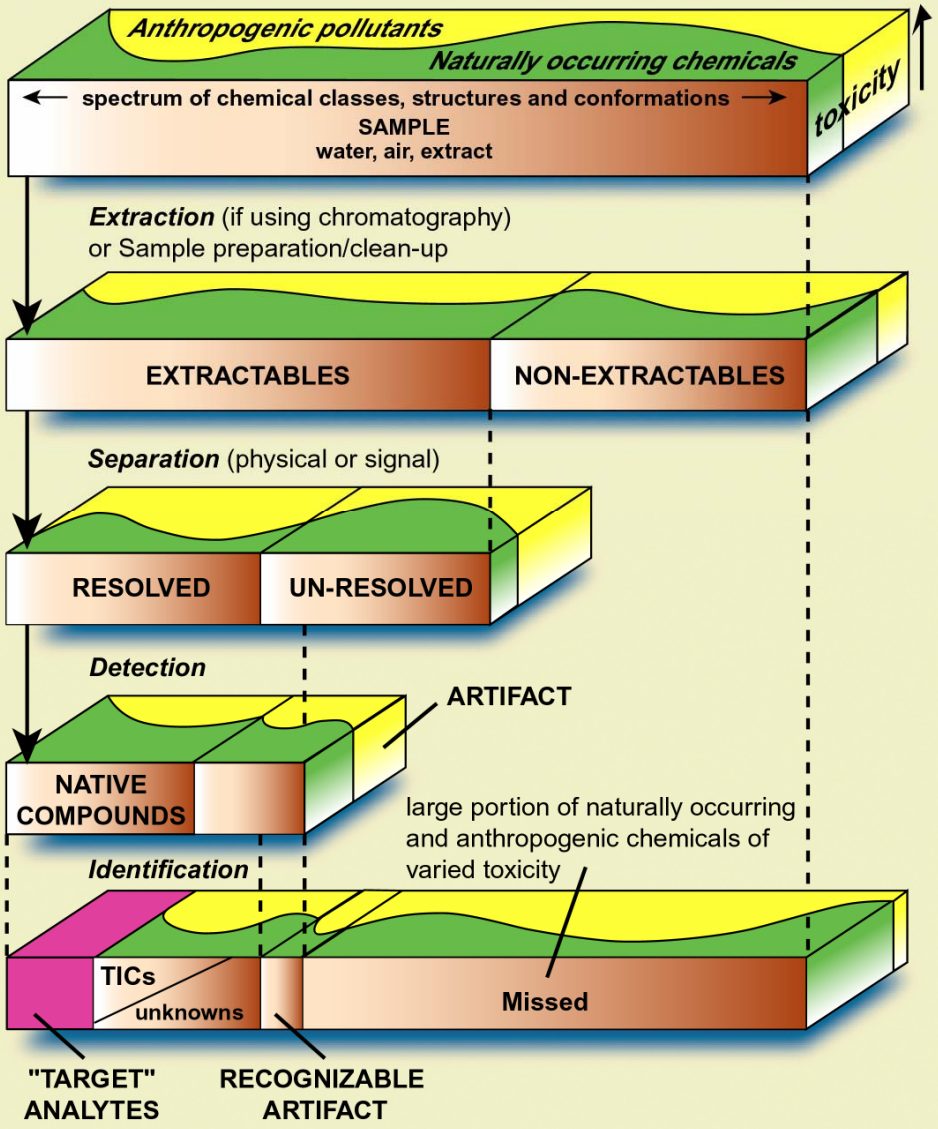
Scope of Issue

- Thousands of distinct chemical entities.
- Numerous (and increasing) therapeutic classes and end uses.
- Large numbers possess very high biological activity.
- Antibiotics (potential for resistance selection among pathogens) and steroidal hormones (overlap with endocrine disrupting chemicals) have received most attention

Scope of issue

- Other classes—little is known regarding the potential for effects.
- In general, PPCPs are not regulated water pollutants (under the Clean Water Act).
- Regulated pollutants compose but a very small piece of the universe of chemical stressors to which organisms can be exposed on a continual basis.

Limitations and Complexity of Environmental Chemical Analysis

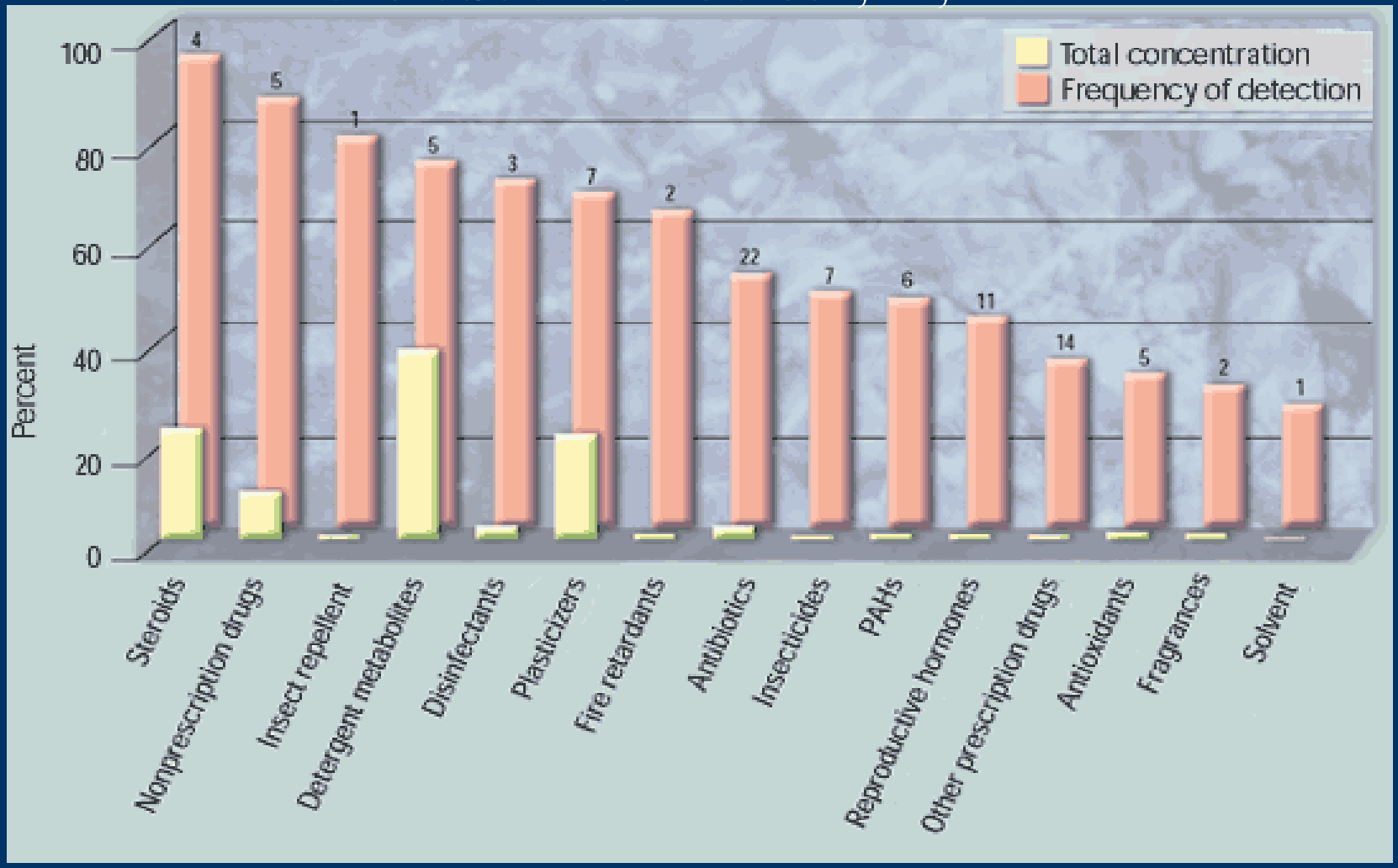


TICs = tentatively identified compounds

C.G. Daughton
U.S. EPA July 2002

274odc02-figure 2

USGS, 1999-2000; 139 streams; 30 states
Examined for 91 contaminants
Environ. Sci. Technol.**2002**, 36,1202-1211



(You can only find what you look for: What's missing?)

Origins of PPCPs in the environmnent

- Sewage treatment plants; raw sewage
  - Human excretion
  - Drug disposal
- Municipal landfills
- Confined animal feeding operations
- Medicated pet excrement
- Aquaculture
- Cruise ships
- Washing of externally applied PPCPs

Determinants of concentrations of pharmaceuticals in water

- Amount sold
- Pharmaco-kinetic behavior in people/animals
- Rates of chemical, microbial, photolytic degradation in environment, including sewage treatment plants

PPCPs in Receiving Waters: A Ubiquitous Process with Unique Local Expression

- ALL municipal sewage, regardless of location, will contain PPCPs. Issue is not unique to any particular municipal area.
- Each geographic area will differ only with respect to the types, quantities, and relative abundance of individual PPCPs.

Frequently detected compounds: Las Vegas wash

- Most frequently detected: caffeine, carbamazepine (used to treat epilepsy), cotinine, and dehydronifedipine (a metabolite of the antianginal Procardia).
- Less frequent: antibiotics (clarithromycin, erythromycin, sulfamethoxazole, and trimethoprim), acetaminophen, cimetidine, codeine, diltiazem (an antihypertensive), and 1,7-dimethylxanthine (a metabolite of caffeine).

Removal of Antibiotics from Surface and Distilled Water in Conventional Water Treatment Processes. J. Envir. Engrg., 128 (3) 253-260, 2002.
Adams, et al.

Conventional drinking water treatment processes were evaluated under typical water treatment plant conditions to determine their effectiveness in the removal of seven common antibiotics: carbadox, sulfachlorpyridazine, sulfadimethoxine, sulfamerazine, sulfamethazine, sulfathiazole, and trimethoprim. Experiments were conducted using synthetic solutions prepared by spiking both distilled/deionized water and Missouri River water with the studied compounds. Sorption on powdered activated carbon, reverse osmosis, and oxidation with chlorine and ozone under typical plant conditions were all shown to be effective in removing studied antibiotics. Conversely, coagulation/flocculation/sedimentation with alum and iron salts, excess lime/soda ash softening, ultraviolet irradiation at disinfection dosages, and ion exchange were all relatively ineffective methods of antibiotic removal. This study shows that the studied antibiotics could be effectively removed using processes already in use in many water treatment plants. Additional work is needed on by-product formation and the removal of other classes of antibiotics.

Environmental Toxicology and Chemistry: 22: 2872–2880, 2003.

OCCURRENCE OF NEUTRAL AND ACIDIC DRUGS IN THE EFFLUENTS OF CANADIAN SEWAGE TREATMENT PLANTS

Metcalfe et al.

	Influent samples				Effluent samples			
Compound	LOD (μg/L)	Median (μg/L)	Max. (μg/L)	Number ND	LOD (μg/L)	Median (μg/L)	Max. (μg/L)	Number ND
Acidic drugs								
Salicylic acid	0.25	330*	874*	0	0.10	3.6	59.6	12
Ibuprofen	0.10	38.7	75.8	4	0.05	4.0	24.6	6
Fenoprofen	0.10	1.8	9.7	9	0.05	ND	—	18
Ketoprofen	0.10	5.7	5.7	17	0.05	ND	—	18
Diclofenac	0.50	1.3	1.3	17	0.25	ND	—	18
Naproxen	0.25	40.7*	611*	2	0.10	12.5	33.9	15
Bezafibrate	0.10	0.6	4.7	10	0.05	0.2	0.6	15
Gemfibrozil	0.10	0.7	2.1	15	0.05	1.3	1.3	17
Clofibric acid	0.10	ND	—	18	0.05	ND	—	18
Neutral drugs								
Phenazone	0.50	ND	—	18	0.10	ND	—	18
Pentoxyfylline	1.0	ND	—	18	0.25	0.5	0.6	14
Carbamazepine	0.50	0.7	1.9	0	0.10	0.7	2.3	0
Ifosfamide	0.50	ND	—	18	0.10	ND	—	18
Cyclophosphamide	0.50	ND	—	18	0.10	ND	—	18

An increasing problem

- Estimates of global increase in population 1 billion/decade x current annual increase in drug consumption 3 % = threefold increase in drug consumption in 25 years with increasing pressures on the same amount of water

2006 = 

2030 = 

Aquatic organisms — continual, life-cycle chemical exposures

- Chemicals continually infused to the aquatic environment essentially become "persistent" pollutants even if their half-lives are short — continually replenished

- Any chemical introduced via sewage to the aquatic environment can lead to continual, multigenerational exposure for aquatic organisms.

Bioconcentration: New Concerns ?

• Traditionally, bioconcentration thought related to octanol:water coefficient; e.g. synthetic musks, sunscreens, parabens, triclosan

•Low octanol-water partition coefficients (high polarity) would seem to preclude bioconcentration for most PPCPs.

•But certain drugs, despite low lipid solubilities, are being detected in aquatic tissues in concentrations higher than those in the ambient water. This is perhaps partly a result of drugs being designed to take advantage of gaining intracellular access via active transport :

Examples:

estrogens (concentrated in fish bile 60,000 X)
gemfibrozil (concentrated in fish tissue, 113 X)
diclofenac (concentrated in fish)
fluoxetine (concentrated in muscle, liver, and brain of fish)

Potential impacts of PPCPs in the environment

- Exposure from environmental sources at therapeutic doses is NOT the concern.
- Exposure to non-target organisms could be significant.
- Continual input via treated sewage imparts PPCPs with "pseudo-persistence" even if they have short half-lives.
- Aquatic organisms can suffer continual exposure.

Potential impacts (cont)

- Subtle effects (e.g., neurobehavioral change; reproductive impacts), even at ppb levels (µg/L).
- Effects from simultaneous exposure to multiple chemical stressors over long periods of time.
- Potential for additive (cumulative) and interactive (synergistic) effects from multiple exposures—same and different mechanisms of action.

Potential Impacts (cont)

- Comparatively little research performed at extremely low concentrations (nM-pM and below). Some agents have ability to impart previously unrecognized effects at "ultra-trace" concentrations.

- Non-target species receptors not well characterized. Variation in receptors across species, and unknown overlap with humans leads to questions regarding potential effects.

Potential Impacts (cont)

- Genetic susceptibility within species.
- MOAs not fully understood. Even most drugs can each have a multitude of effects. Most MOAs for the therapeutic endpoints, however, remain to be discovered, even for humans.

Endocrine disrupting effects

- Feminization of male fish—identified in rivers in many parts of the world (vitellogenin synthesis as a marker in addition to anatomic changes)
- Concern about endocrine disrupting effects on population dynamics

Acetaminophen for control of Brown Tree snakes

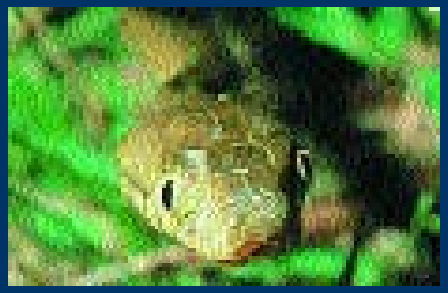
Brown Tree snakes (*Boiga irregularis*), native to eastern Indonesia, become invasive pests on Guam starting in the 1940's/1950's.

Without natural predators, the Brown Tree snake's population in Guam is estimated at upwards of 15,000 per square mile.

Have decimated certain native bird, bat, and reptile populations, as well as caused extensive economic losses (agriculture, pets, human bites, electric grid outages/repairs).

No safe and effective chemical-controls until discovery by USDA that **acetaminophen (80 mg) will effectively kill Brown Tree snakes within 3 days** of even a brief exposure to baited, dead mice.

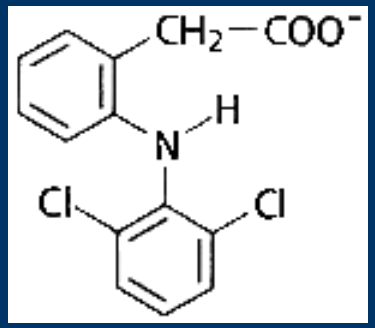
Acute effects of larger doses of acetaminophen on local non-target species have not been detected.



[see: J. J. Johnston et al. "Risk Assessment of an Acetaminophen Baiting Program for Chemical Control of Brown Tree Snakes on Guam: Evaluation of Baits, Snake Residues, and Potential Primary and Secondary Hazards," *Environ. Sci. Technol*. 2002, 36(17):3827-3833; also: http://www.aphis.usda.gov/lpa/inside_aphis/features10d.html].

Decline of *Gyps* spp. Vultures in Pakistan & India – Possible Link with Diclofenac

- Beginning in the early 1990s, vultures (especially white-backed vultures such as *Gyps bengalensis*) have experienced dramatic population declines (as great as 95%) in Southern Asia – particularly India and spreading to Pakistan and Nepal.
- Various hypothesized causes have ranged from pathogens to pesticides. The causative agent(s) result in acute renal failure (manifested as visceral gout from accumulation of uric acid), leading to death of the breeding population.
- Prof. J. Lindsay Oaks (Washington State University) et al. present evidence that (at least in Pakistan) the die-offs are strongly linked with **diclofenac** poisoning ("Diclofenac Residues as the Cause of Vulture Population Decline in Pakistan," *Nature*, 28 January 2004).
- Diclofenac, although primarily a human NSAID, is used in veterinary medicine in certain countries. In India, diclofenac is used for cattle, whose carcasses are a major food source for *Gyps*.



- Diclofenac seems to be selectively toxic to *Gyps* spp. versus other carrion-eating raptors.
- Health hazards grow from the accumulation of uneaten cattle carcasses (as well as human), which now serve to attract growing packs of dangerous feral dogs, which can also carry rabies. As of 2005, India will phase-out the veterinary use of diclofenac.

Potential for Unrecognized Effects?

- ? Allergic reactions in sensitive humans—a theoretical possibility

- Biological actions on non-target species may be imperceptible initially but lead to adverse impacts as a result of continual exposure over time.

- Effects that are sufficiently subtle that they are undetectable or unnoticed present a challenge to risk assessment (especially ecological) — e.g., subtle shifts in behavior or intelligence.

Subtle, Difficult-to-Detect Effects:
some examples

- Profound effects on development, spawning, and other behaviors in shellfish, ciliates, and other aquatic organisms by SSRI and tricyclic antidepressants (ppb levels).
- Dramatic inhibition of sperm activity in certain aquatic organisms by calcium-channel blockers.
- Antiepileptic drugs (e.g., phenytoin, valproate, carbamazepine) have potential as human neuroteratogens, triggering apoptosis in the developing brain → neurodegeneration.

Subtle, Difficult-to-Detect Effects

- ppm and sub-ppm levels of various drugs (NSAIDS, glucocorticoids, anti-fibrotics) affect collagen metabolism in teleost fish, leading to defective/blocked fin regeneration

- Multi-drug transporters (efflux pumps) are common defensive strategies for aquatic biota
  - ?? significance of efflux pump inhibitors in aquatic organisms?

Summary

- Residues of pharmaceuticals reach SPTs via the sewer system. In the STPs they are removed or degraded to various extents.

- Effluents from STPs contain pharmaceuticals, which are diluted in the recipient. If the recipient is used as a tap water source low concentrations of pharmaceuticals may reach consumers via the tap water.

Summary (cont)

- These concentrations of pharmaceuticals are too low to cause a ”therapeutic” effect.
- The ecological and human health consequences of a lifelong exposure to mixtures of low levels of pharmaceuticals are, however, unknown. Furthermore, limited experimental methods are available to evaluate such consequences.

end

European efforts

- European Medicines Agency (EMEA) has issued draft guidelines
- Sweden has prioritized pharmaceuticals in the environment as a national environmental concern
- Stockholm County Council has taken a leadership role

Stockholm County Council

- Pollution of ground, water, and air with residues of pharmaceutical drugs is among the top five environmental priorities

Stockholm County Council

- Vision: County Council activities should not add any persisting drug residues to the ground, water, or atmosphere
- Periodic goal: In 2006, all County Council health care services will have adopted action plans for diminishing pollution of ground, water, and air with residues of pharmaceutical drugs.

Factors to consider

- Amount sold annually
- Ecological half-life
- Recipient volume (e.g. water body)
- Eco-toxicity
- Bioavailability
- Bioaccumulation
- Constituents
- Inappropriate packaging

Stockholm County Council model

- Collaboration among SCC, Apoteket AB, and ecotoxicological experts
- Considers: persistence, bioaccumulation, toxicity to aquatic organisms.
- Each property assigned a value on a scale from 0-3. The sum of these values is the PBT index.

SCC model

- Biodegradability based on OECD test 301 or other equivalent test.
- Bioaccumulation based on OECD 107 or 117 (o/w partition coefficient) or on actual test data.
- Toxicity at three trophic levels: fish, daphnia, algae (OECD 203, 202, 201)
- Worst case assumption when no data

Toxicity classification

- LC/EC/IC50 < 1 mg/l; very high toxicity
- LC/EC/IC50 1-10 mg/l; high toxicity
- LC/EC/IC50 10-100 mg/l; moderate toxicity
- LC/EC/IC50 >100 mg/l; low toxicity

SCC model

- Defined daily dose (DDD): estimated average administered dose per day when used for the drug's main indication
- Note that the number of DDDs does not necessarily correlate with quantity of active substance in kilograms.

ENVIRONMENTALLY CLASSIFIED PHARMACEUTICALS 2005

PBT index

* Data gap

DDD

M Musculoskeletal system

Anti-inflammatory and anti-rheumatic agents

Diclofenac	7	6 484 198
Tenoxicam	4	192 680
Ibuprofen	5	9 555 847
Naproxen	7	3 666 094
Ketoprofen	7*	1 973 231
Valdecoxib	9*	167 740

SCC recommendations

- Follow SCC's "wise list" of recommended drugs for common diseases
- When medical efficacy, safety, and price are comparable, use the drug posing the lowest environmental risk
- Prescribe starter packs.
- Encourage patients to return unused drugs to pharmacy

SCC recommendations

- Inform patients that even used estrogen patches contain estrogen that should not be discarded to water
- Do not prescribe more than can be used
- Review patients' total use of medications
- Read the Swedish Medical Products Agency study "Environmental Impacts from medications, cosmetics, and hygienic products"

Resources

- http://www.janusinfo.se/imcms/servlet/GetDoc?meta_id=7242 SCC Brochure
- http://www.janusinfo.se/imcms/servlet/GetDoc?meta_id=7236 SCC home page on pharmaceuticals and environment
- http://www.emea.eu.int/pdfs/human/swp/444700en.pdf EMEA draft guideline for risk assessment of pharmaceuticals for human use